

Review

Quantitative aspects of stress-induced immunomodulation

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Abstract

Recent studies indicate that neuroendocrine–immune interactions can cause sufficient immunosuppression to adversely affect human health, but quantitative relationships between stress-related hormones or neurotransmitters and immune function have not been well documented. The mechanisms of stress-induced immunomodulation cannot be fully understood solely by identifying the hormones, neurotransmitters, and cytokines involved. Quantitative relationships and interactions must also be understood. Depending on the nature and duration of the stressor and the immunological parameter under investigation, stress responses can enhance, have no effect, or suppress immunological parameters. These quantitative relationships have implications with regard to safety assessment of drugs and chemicals and with regard to potential development of pharmacological interventions to ameliorate some of the immunosuppressive effects of stress. This review describes selected studies that relate the quantity and duration of exposure to stress-related neuroendocrine mediators to modulation of the immune system. These studies provide a useful starting point, but they also illustrate how much work remains to achieve a fully integrated qualitative and quantitative understanding of stress-induced immunomodulation. © 2001 Elsevier Science B.V. All rights reserved.

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1. Quantitative aspects of neuroendocrine–immune interactions: important but neglected

Recent evidence clearly illustrates that neuroendocrine–immune interactions can affect the immune system in humans to a sufficient degree to diminish the effectiveness of vaccines and to increase the severity of infections [1–3]. Psychogenic stress can be a potent inducer of neuroendocrine mediators that suppress the immune system, and most studies have

focused on these neurotransmitters and hormones and on the subsequent signaling pathways [4–6]. Such studies have increased the credibility of this field of study by unequivocally demonstrating mechanisms by which the neuroendocrine and immune systems can influence each other [7,8]. The importance of these mechanisms in maintaining homeostasis in health and in a variety of disease states is now becoming apparent. Strong relationships have been reported between one or more stress-related hormones and normal development of T cells in the thymus [9,10], development of autoimmune diseases [11,12], exacerbation of autoimmune diseases [13], feedback control of a potentially lethal cytokine-in-

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duced shock syndrome [14], and even enhancement of some immunological responses following brief or mild stressors [15,16]. Stress-induced increases in glucocorticoids have also been implicated in cell death in the brain which may contribute to learning and memory deficits associated with stress and related psychological conditions [17]. Thus, there is considerable interest in pharmacological or psychological intervention to ameliorate the harmful effects of stress. However, it is possible that such interventions would also interfere with some of the beneficial effects of stress-related mediators, such as protection from cytokine-mediated shock syndrome or prevention of autoimmunity. However, the quantity and duration of increased stress hormone levels required for beneficial effects as compared to those required

for immunosuppressive or neurotoxic effects have not typically been compared in the same experimental system. Therefore, it is difficult to generalize from available data regarding quantitative aspects of beneficial and harmful effects of stress responses. Although it should be possible to predict the magnitude of immunological changes in response to stressors on the basis of the changes in concentration of immunomodulatory neuroendocrine hormones, a number of other factors can influence immunological outcomes and these factors may have obscured underlying quantitative relationships (Fig. 1).

It might be expected that the immune system of rat or mouse strains with constitutively high levels of corticosterone would adapt, for example, by down-regulating glucocorticoid receptor number or affinity,

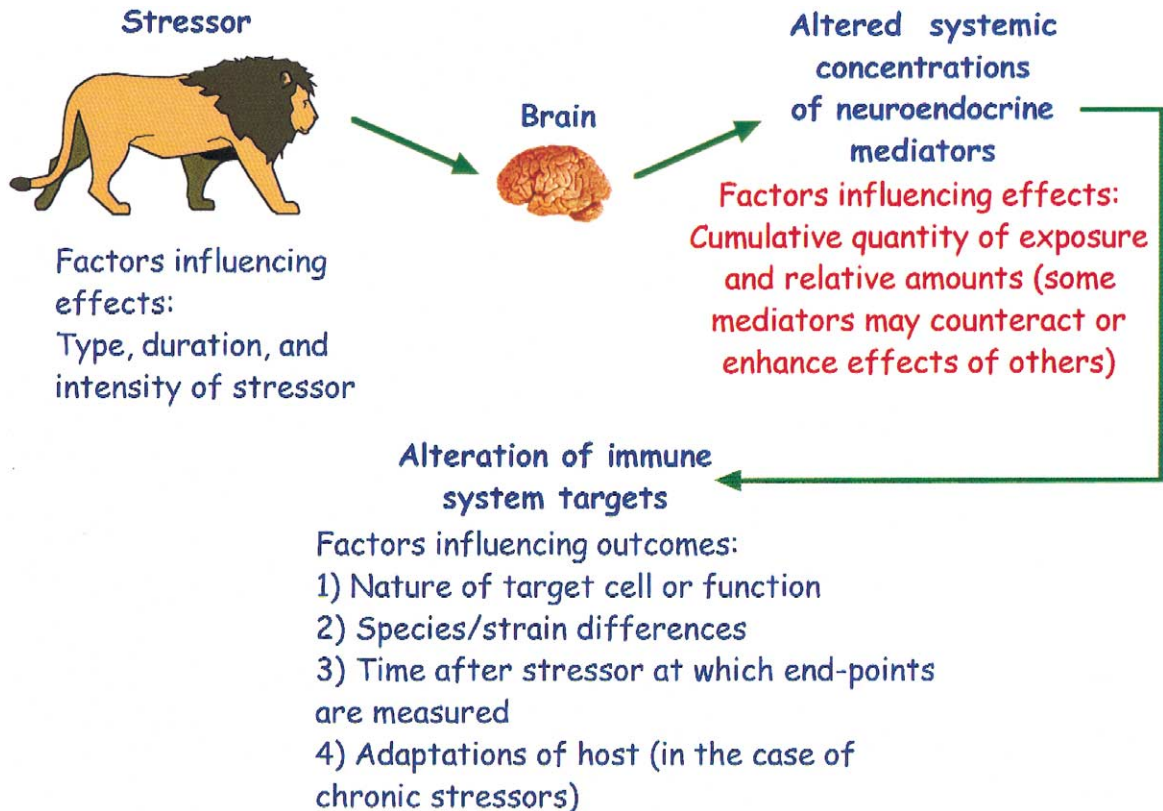


Fig. 1. An overview of the effects of stressors on the immune system. Although many factors influence the effects of stressors on the immune system, the cumulative quantity of neuroendocrine mediators to which cells of the immune system are exposed is a central factor (shown in red). This has sometimes been obscured by the other factors listed, which vary considerably among different experimental systems. However, evidence cited in this review suggests that quantitative assessment of a single neuroendocrine mediator may be sufficient to predict immunological outcomes.

to prevent excessive effects of glucocorticoids. However, thorough investigation of these parameters in Fisher 344 rats (which have constitutively high corticosterone concentrations) and Lewis rats (which have low corticosterone concentrations) did not reveal such changes [18]. Concentrations of corticosteroid binding globulin (CBG) in the serum may change in response to some stressors [19], and this may alter the bioavailability of glucocorticoids. However, it is not clear that increased CBG levels always decrease the accessibility of corticosterone to all cell types [20]. In addition, we noted that restraint stress and administration of corticosterone to produce stress-inducible blood levels did not substantially affect the percentage of bound vs. free corticosterone in the serum [21]. Thus, a stress response sufficient to suppress the immune system does not necessarily cause substantial alterations in the level of corticosterone binding proteins. Concentrations of 11- β hydroxysteroid dehydrogenase (which degrades glucocorticoids) are regulated in various tissues [17]. In addition, it has been suggested that dehydroepiandrosterone (DHEA) can counter the effects of corticosterone and other glucocorticoids and that this adrenal steroid might be important in regulating stress responses [22]. However, mice and rats produce very low levels of DHEA [23,24]. Therefore, the relevance of the effects of exogenous DHEA in mouse and rat models is unclear. Similarly, results from studies involving synthetic glucocorticoids are often generalized, and it is assumed that these results also apply to stress-induced increases in natural glucocorticoids. Unfortunately, there are differences in the distribution of natural and synthetic glucocorticoids to immune tissues, and there are differences in the relative binding affinity for type I (mineralocorticoid) and type II (glucocorticoid) receptors, which may have functional implications [25,26]. In any case, the extent to which these potentially important regulatory factors influence the effects of stressors on the immune system is not clear, and these issues are not considered in many studies.

There is a surprising paucity of quantitative data on neuroendocrine-immune interactions. Although a variety of effective approaches have been used to determine that particular neuroendocrine mediators can affect the immune system, very few studies have investigated the level of exposure to particular neu-

roendocrine mediators required to produce a particular quantity of change in immunological parameters. In most studies, a single type and duration of stressor is used and the concentrations and kinetics of neuroendocrine mediators are not measured. Thus, quantitative relationships between the type and duration of stressor, changes in the concentrations of neuroendocrine mediators, and changes in immunological parameters are not typically known. This lack of quantitative data represents a fundamental gap in the understanding of neuroendocrine-immune interactions. This is perhaps best illustrated by the observation that there are only a few experimental systems for which sufficient data are available to allow prediction of immunological changes on the basis of measured changes in the concentrations of one or more neuroendocrine mediators.

There is also a surprising lack of information regarding the chronic effects of stressors on the immune system. As already mentioned, glucocorticoid receptors are apparently not downregulated in response to chronically high concentrations of glucocorticoids. A recent report suggests that immobilization stress actually increases the number of glucocorticoid receptors in the cytoplasm [27]. Only a few studies have been done in which the effect of acute and chronic stress on the immune system have been compared, and evidence has been presented both for and against adaptation [28–31]. Because chronic elevation of stress-related hormones is associated with continued suppression of a variety of immunological parameters, including host resistance to infection [2,3,32–34], it seems unlikely that immune system targets of these hormones can become substantially less sensitive to their effects. However, habituation can decrease the neuroendocrine response to stressors, and this may explain some cases of apparent adaptive responses of the immune system to stressors [30,31].

At the molecular level, most studies have been conducted using *ex vivo* or *in vitro* approaches, and efforts to correlate molecular signaling mechanisms with immunological changes *in vivo* have been rare. Lymphocytes and other cell types in the immune system have receptors for glucocorticoids, catecholamines, opiates, and other neuroendocrine mediators [4]. However, results comparing the dose-response profile for signaling parameters and for immunologi-

cal end points *in vivo* are not available. Thus, it remains possible that signaling systems that have been implicated in the effects of neuroendocrine mediators on the immune system [35,36] may not be as important as assumed and that other signaling systems may predominate in typical stress responses *in vivo*.

The relatively small number of studies that have emphasized or carefully considered quantitative aspects of stress-induced immunomodulation have revealed useful information and suggest productive directions for future work, and this review summarizes some of these studies.

2. Quantitative aspects of beneficial effects of stress or stress hormones on the immune system

Low concentrations of corticosterone (~ 0.35 ng/ml as compared to > 20 ng/ml in circulation in mice) seem to be required for normal development of T cells in the thymus, and corticosterone can be produced locally in the thymus in mice [37,38]. It has been suggested that this local production is important during fetal development, when production of corticosterone by the adrenal glands has not begun and circulating levels are very low. In the absence of glucocorticoids (in fetal thymus organ cultures), thymocytes that interact with stromal cells with sufficient avidity for positive selection are not positively selected, but die by apoptosis [37]. Using transgenic mice that express an antisense mRNA for glucocorticoid receptor only in developing T cells, Lu et al. [9] demonstrated that hyporesponsiveness to corticosterone in these cells leads to a “hole” in the T cell repertoire. This may be caused by the same decreased sensitivity of thymocytes to positive selection signals that leads to hypoplasia in the fetal thymus when insufficient concentrations of glucocorticoids are present. However, in knockout mice that lack the selecting MHC gene products, suppression of corticosterone synthesis using metyrapone actually enhances survival of these cells that are all destined to die by neglect (not by negative selection) [37]. Thus, it seems possible that glucocorticoids may contribute to death by neglect in those thymocytes that are not positively or negatively selected. More recently, however, fundamental questions have

been raised about the role of glucocorticoids in T cell development. Thymocytes apparently develop normally in transgenic knockout mice that lack functional glucocorticoid receptors [39]. Although these mice die at birth due to defective lung development, thymic development up to embryonic day 18 is normal, and subsequent development in fetal thymus organ cultures also does not differ significantly from that observed in cultures from normal mice. The basis for the discrepancies in this study and previous studies is not clear. Caution is in order in interpreting data from knockout mice, because the absence of glucocorticoid signaling throughout development could have triggered compensatory mechanisms that obviate the need for glucocorticoids in thymic development. In addition, it is possible that elimination of enhancing and suppressive effects of glucocorticoids [17] on different functions required for development of T cells in the thymus could lead to essentially no change in the parameters measured. In any case, a quantitative understanding of the effects of glucocorticoids on the thymus remains of interest not only with regard to T cell development in the thymus but also because stressors induce thymic atrophy in mice and humans [40,41].

Placing a GR anti-sense gene in MRL/lpr autoimmune prone mice decreased autoimmune disease. Thus, a decreased response to glucocorticoids decreases the development of autoimmune disease in this particular model [42]. However, this contradicts the conclusion reached by several labs that rat or mouse strains with high basal and stress-induced levels of corticosterone have a substantially lower incidence of autoimmune disease than strains with low levels [12]. The basis for this contradiction is not clear, but it is possible that low corticosterone concentrations only decrease the immune repertoire if they occur during development or early in post-natal life. Later in life, the high corticosterone levels noted in some strains may act to diminish the initiation or the effector phase of autoimmune diseases. In any case, more detailed quantitative studies are needed to determine if the differences in corticosterone concentration between strains is sufficient to account for differences in initiation or severity of autoimmune disease.

Recent evidence suggests that basal levels of corticosterone are sufficient to prevent cytokine-induced

death in mice infected with murine cytomegalovirus [14]. However, basal concentrations of corticosterone are not sufficient to protect mice from the development of experimental allergic encephalomyelitis; stress-induced levels are required [17,43]. Thus, the level of corticosterone required to provide protection from detrimental immune responses may depend on the nature of the immune response.

Mild or relatively brief stress responses can enhance or have no effect on some immune responses or functions [44]. For example, exercise causes an increase in the number and function of NK cells in the blood [45,46]. This seems to be mediated primarily by catecholamines [46,47]. Acute administration of cocaine induces a brief stress response in mice, and the corticosterone induced in this response is associated with an enhanced humoral immune response to a T-dependent antigen [16]. Brief (1 h) restraint stress causes profound changes in lymphocyte recirculation patterns in rats [48]. There is a transient lymphopenia as lymphocytes migrate from the blood to tissues. Concomitantly, there is an enhanced delayed hypersensitivity response in the skin [49]. In a previous review, we noted that brief duration of stress and evaluation of immunological parameters (or removal of cells for *ex vivo* analysis) less than ~6 h after the stressor is not generally immunosuppressive and may cause immunoenhancement [44]. The benefit to the host of these physiological responses is not clear, but it has been suggested that altered recirculation patterns represent a realignment of cellular duties from “patrol” to “battle stations” in response to an anticipated immunological challenge that would accompany injury [48]. Interestingly, some of the same stimuli (e.g., exercise) can produce an early enhancement of immune function followed at a later time by suppression of the same parameters [45]. Direct infusion of mediators to produce stress-inducible concentrations *in vivo* or the use of antagonists to block the action of particular mediators suggest that both glucocorticoids and catecholamines are important in the acute redistribution of leukocytes noted after stress [47,48].

Daynes and Araneo [50] first reported that glucocorticoids suppress Th2 responses but enhance Th1 responses in mice. This has obvious implications with regard to the regulation of hypersensitivity and allergy as well as beneficial immune responses to

microorganisms. Although the initial study utilized a synthetic glucocorticoid, other studies using natural glucocorticoids at stress-inducible levels have yielded similar results [22,51]. However, other investigators have not found preferential suppression of the production of Th1 cytokines by glucocorticoids [52–55]. The basis for the differences in these results is not clear, but the type of glucocorticoid, concentrations in the blood (or dose), and the duration of increased glucocorticoid concentration were not the same in all studies. It remains possible that quantitative differences in glucocorticoids along with other mediators may account for some of the disparity in these results.

3. Quantitative aspects of deleterious effects stress or stress hormones on the immune system

In contrast to the beneficial effects often noted after exposure to mild or brief stressors, suppression of a wide variety of immunological parameters is consistently reported in response to intense stressors or prolonged exposure to stressors [56–60]. Fig. 2 illustrates the marked difference between corticosterone exposures associated with immunoenhancement (induced by cocaine or brief restraint) and exposures associated with immunosuppression (induced by a timed-release morphine pellet or exogenous corticosterone). Thus, results previously interpreted as indicating that stress-induced glucocorticoids are not immunosuppressive [65,66], may only reflect quantitative differences in exposure to neuroendocrine mediators. Suppression of antibody responses [59], NK cell activity [67], and the number of lymphocytes in the spleen or thymus [64,68] are typically noted following intense or long-term stress. Brief or mild stress can enhance cellular [49] or humoral [16] immune responses.

Although catecholamines, endogenous opiates, and a variety of other hormones and neurotransmitters can affect the immune system, much less is known about quantitative aspects of their effects than for glucocorticoids. In the case of catecholamines, it is technically difficult to obtain blood samples from rodents without increasing catecholamine concentrations as a result of handling and bleeding. The same

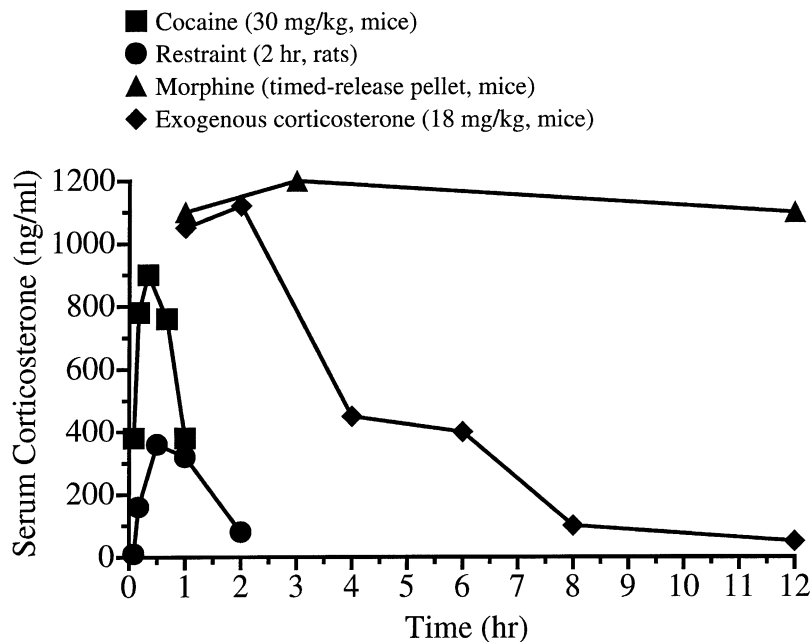


Fig. 2. Comparison of the effects of immunosuppressive and immunoenhancing stressors on serum corticosterone concentrations. Cocaine enhances the humoral response to sheep erythrocytes [16]. The corticosterone values for restraint in rats are adapted from Dhabhar et al. [48], and these investigators noted that this treatment enhances cell-mediated immunity [61]. Implantation of timed release morphine pellet profoundly suppresses a wide range of immunological parameters [62]. Exogenous corticosterone (18 mg/kg) also suppresses a wide range of immunological parameters in mice [21,63,64].

applies to most other stress-related mediators that are released rapidly (within several seconds) after stress [17]. However, studies involving administration of exogenous mediators or antagonists have indicated a role for several of them in stress-induced immunosuppression. In a particularly instructive study, Marotti et al. [69] found that different immunological parameters are suppressed by activation of the hypothalamic–pituitary–adrenal axis, opiates, and other mediators (possibly catecholamines) during the same response to restraint stress in mice.

The effects of stress on some immune parameters are complex, and their relationship to the intensity or duration of the stressor is not clear. For example, the ability of natural killer (NK) cells to lyse tumor targets can be suppressed by intense, prolonged stress responses [62,67] or by mild, brief stress [70,71]. Exercise stress seems to exert a biphasic effect on NK cell numbers and activity characterized by a rapid increase in number in the circulation followed by a more prolonged decrease [45]. This may reflect differences in the kinetics of action of different

neuroendocrine mediators. We noted that both catecholamines and glucocorticoids seem to contribute to suppressed NK cell activity in mice subjected to the stress response caused by a single dose of ethanol [72–74]. Administration of exogenous corticosterone to produce an area under the corticosterone concentration vs. time curve (AUC) comparable to that measured in mice treated with ethanol suppressed NK cell activity. Also, a glucocorticoid antagonist partially blocked ethanol-induced suppression of NK cell activity. Complete prevention of the effects of ethanol could only be achieved with a combination of glucocorticoid and β -adrenergic antagonists, suggesting a role for both glucocorticoids and catecholamines. However, the more prolonged stress response associated with implantation of a timed-release morphine pellet suppressed NK cell activity by a completely corticosterone-dependent mechanism [67]. Thus, the relative importance of different neuroendocrine mediators responsible for stress-induced immunosuppression seems to depend on the intensity and duration of the stress response.

Chronic or intense stress suppresses immune function to a sufficient degree to decrease resistance to infection or cancer. For example, suppressed resistance to influenza virus is noted in mice subjected to restraint stress [75]. Even relatively mild stress can suppress resistance to tumor cells in some models [76]. Acute administration of ethanol suppresses resistance to B16F10 tumor metastases in the lung in mice. This effect was decreased by a glucocorticoid antagonist (RU 486) and decreased to a greater extent by adrenalectomy, indicating an important role for glucocorticoids and probably catecholamines as well [77].

Uncertainties remain as to the major neuroendocrine mediator involved in some stress-related effects on the immune system. For example, convincing evidence has been presented for a primary role for endogenous opiates in splenocyte apoptosis and splenic atrophy induced by restraint [34], whereas glucocorticoids seem to be the major mediator of apoptosis and splenic atrophy in mice treated with a chemical stressor [78]. This could indicate that different stressors work through different mediators. However, mouse strain differences should never be overlooked in studies of the neuroendocrine-immune axis. This is illustrated by the finding that morphine acts directly through opiate receptors on splenocytes to suppress humoral responses in B6C3F1 mice from one supplier [79], whereas it acts indirectly by increasing corticosterone concentrations in B6C3F1 mice from a different supplier [80]. Further investigation of these strains revealed that they had been maintained separately for more than 4 decades and apparently had diverged during that time in terms of the mode by which they respond to morphine [79].

4. Quantitative aspects of the effects of stress or stress-related hormones in humans

Changes in lymphocyte concentration in the blood in response to glucocorticoids have been described using pharmacokinetic/pharmacodynamic modeling. Relatively small changes in the normal circadian pattern of lymphocyte concentration could be predicted on the basis of the concentrations of endogenous cortisol and of an exogenous synthetic gluco-

corticoid [81]. Decreased numbers of lymphocytes and increased numbers of neutrophils in the blood are characteristic of stress responses. The ability to model relatively small changes in these parameters demonstrates the feasibility of developing quantitative models that can be used to predict immunological effects on the basis of cumulative exposure to a neuroendocrine mediator. Similar results have been reported in rats [48]. A single dose of cortisol to produce transient stress-inducible levels causes lymphocytosis and suppresses *ex vivo* production of TNF- α [82]. Similar results have been noted in a mouse model [83]. Together, these results indicate that stress responses or individual hormones at stress-inducible levels can significantly suppress a number of immunological parameters in humans.

Stress caused by surgery, trauma, or burn injury is associated with suppression of a number of immunological parameters. In a particularly well-designed study, Blazar et al. [84] demonstrated a cause-effect relationship between elevated concentrations of circulating stress hormones or neurotransmitters (cortisol, epinephrine, and glucagon) and suppression of NK cell activity in humans. The hormones were administered by continuous infusion, to produce concentrations comparable to those measured in trauma patients. In another study, increased neutrophil mobilization and decreased chemotaxis were noted after infusions of cortisol and epinephrine to produce stress-inducible concentrations [85]. Decreased expression of MHC class II proteins on the surface of monocytes has also been noted in humans subjected to surgical stress. The lowest levels of MHC II expression were noted in patients who ultimately died of infection [86]. Brain trauma and brain surgery also decrease the expression of MHC class II proteins on monocytes, and this is associated with an increased risk of infection [87,88]. It is interesting that chemical-induced stress or restraint stress for a few hours in mice is also associated with decreased MHC II expression on macrophages and B lymphocytes [21,89]. Thus, the effects of severe stressors on MHC class II expression in humans and rodents seem comparable, although the data available do not permit precise quantitative comparisons of mice and humans with regard to hormone levels and decreased MHC II expression. Interestingly, suppression of MHC class II expression during trauma may also be

beneficial, because it may limit induction of responses to autoantigens by macrophages that have cleared dead or dying cells from sites of tissue injury.

Direct administration of epinephrine or norepinephrine increases the number and activity of NK cells in the blood in humans [47]. This was also observed in persons who had previously had a splenectomy [47]. Thus, mobilization of NK cells from locations other than the spleen is sufficient to increase the number of NK cells in the blood. Depression and Cushing's syndrome are associated with elevated serum cortisol levels [33,90] and suppressed NK cell function [33,91]. Quantitatively similar suppression of NK cell activity has been noted in mice and humans exposed to intense exercise or to surgery or trauma [84,92–95].

The stress associated with caring for a dementia patient has been shown in 2 studies to correlate with a decreased antibody response to influenza virus vaccine [2,3]. In one of these studies, the area under the concentration vs. time curve for salivary cortisol was determined, and there was an inverse correlation between this value and the antibody titer [3].

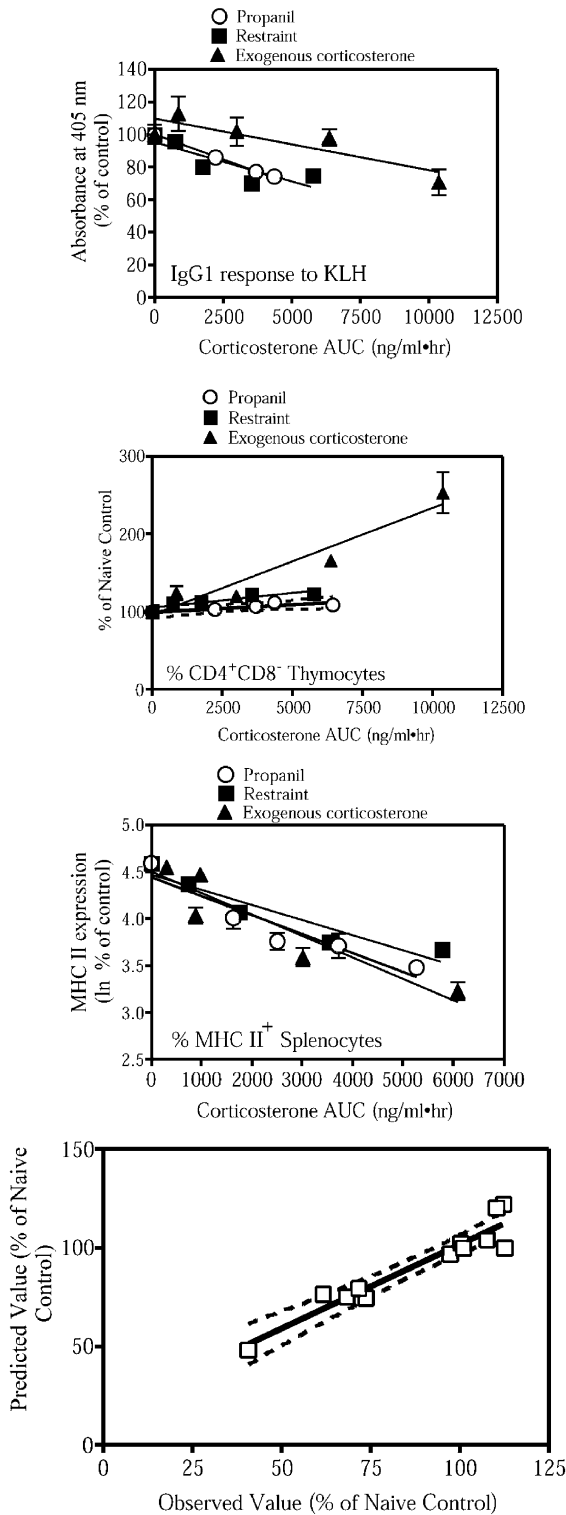
5. Practical implications of quantitative studies of neuroendocrine-immune interactions

Although it is clear that multiple mediators are involved in the effects of stress on the immune system, we have recently found that the immunological effects of a chemical stressor (the herbicide propanil) can be predicted with remarkable precision on the basis of one parameter, cumulative exposure to corticosterone. Corticosterone exposure was measured at several time points and the area under the concentration vs. time curve (AUC) was determined. Linear regression analysis was then used to determine the relationship between corticosterone AUC and various immunological parameters in mice treated with propanil at four different dosage levels. The resultant regression equations were then compared to equations obtained from mice treated with exogenous corticosterone at four dosage levels or restraint for 2, 4, 6, or 8 h. These results are shown in Fig. 3 (adapted from Refs. [63,64,96]. The results

shown are representative of data for 11 immunological parameters tested. Exogenous corticosterone alone suppressed the IgG1 response to KLH to a lesser extent than restraint (at equivalent corticosterone AUC values), suggesting that some of the neuroendocrine mediators induced by restraint stress add to the effects of corticosterone. However, changes in the percentage of lymphocyte subpopulations in the thymus were larger in mice treated with corticosterone than in mice subjected to restraint, suggesting that mediators induced by restraint antagonize this effect of corticosterone. Changes in the expression of MHC class II proteins on the surface of splenocytes (mostly B cells) was essentially the same (at equivalent corticosterone AUC values) in mice treated with exogenous corticosterone and restraint, confirming our previous results indicating that this effect is mediated entirely by corticosterone [89]. Regardless which of these patterns was observed, the effects of propanil were always similar to the effects of restraint. In fact, regression models obtained using restraint could be used to accurately predict the effects of propanil on the 11 immunological parameters tested in these experiments (r^2 for observed vs. predicted = 0.90).

These results do not suggest that corticosterone alone is responsible for the effects of stress on the immune system, but they demonstrate that the effects of disparate stressors might be predictable on the basis of the corticosterone response to those stressors. Thus, corticosterone AUC values may be a useful surrogate for most of the mediators that are induced by stress responses and their effects on the immune system. In addition, the similarity of the effects of restraint and corticosterone on a number of immunological parameters suggest that corticosterone is the major mediator in stress-induced suppression of several important immunological parameters [21,63,96]. A similar conclusion has emerged in our studies with the chemical stressor ethanol [59,89,97].

These results have obvious implications with regard to risk assessment in immunopharmacology and immunotoxicology. The U.S. Environmental Protection Agency (EPA) currently requires immunotoxicological testing of pesticides for new registration, and the guidelines for this testing (OPPTS 870.7800) specify that the highest dose level should produce



signs of generalized toxicity (e.g., 10% decrease in body weight). Many chemicals and drugs can induce a stress response, and this is especially evident when high doses are used [21]. The Food and Drug Administration is considering a similar mandatory immunotoxicity protocol for drugs [98]. Determining the relative importance of the stress response to a drug or chemical in its immunomodulatory effects has important implications in risk assessment. For example, if the stress response accounts for most or all of the immunomodulatory effects in animal models, stress-related hormones could be quantified in humans exposed to the drug or chemical. Absence of a stress response in exposed humans would suggest that the predominant mechanism of immunosuppression in the animal models does not occur in humans and that the risk of immunotoxicity may only occur at doses equivalent to the high levels used in animal testing. However, at present none of the data obtained in a typical safety assessment can be used to determine the degree to which a stress response contributes to immunomodulation. Adrenal hypertrophy can be used as an indicator of stress, but the exact quantitative relationship between adrenal weight and immune parameters has not been determined. If measurements of serum corticosterone concentrations at various times after dosing were included in safety assessment protocols, models such as those shown in Fig. 3 could be used to predict the minimum expected immunomodulation caused by the stress response alone. Of course the chemical could also cause immunomodulation by other mechanisms than the induction of a stress response, so this

Fig. 3. The effects of a chemical stressor can be predicted on the basis of area under the concentration vs. time curve (AUC) for serum corticosterone. These results were adapted from Pruett et al. [64]. They illustrate that corticosterone alone can yield similar or different effects on immune parameters as an equivalent exposure to corticosterone as part of a stress- or chemical-induced stress response. Interestingly, the effects of the chemical stressor (propanil) on the three immunological parameters shown here were similar to those produced by restraint (at equivalent AUC values). This was also true for eight additional parameters. The bottom panel illustrates the use of linear models derived from mice subjected to restraint stress to predict the effects of propanil at 100 mg/kg, based only on the corticosterone AUC value produced by this dosage. The r^2 value for these results is 0.90, indicating excellent agreement between observed and predicted values.

approach would not replace immunological assessments. However, it could be useful in distinguishing non-specific stress effects from direct immunotoxicity.

As already noted, glucocorticoids are not the only mediators involved in stress-induced immunomodulation, but for many immunological parameters they are major contributors. Glucocorticoids have also been implicated in the memory loss and learning deficits often associated with some stressors, particularly in persons with post-traumatic stress disorder. Although it has been difficult to document and quantify increased cortisol levels following exposure to stressors in humans, hints of cortisol-related memory deficits in persons with chronic stress responses have been reported [99]. Chronic or acute therapeutic administration of glucocorticoids has clear adverse effects on memory [100,101]. Animal models have provided substantial evidence for detrimental effects of stress-inducible levels of glucocorticoids on memory formation [102]. Sapolsky et al. [17] have noted in an excellent review that stress-induced glucocorticoids exert several physiological influences. They characterize these influences as permissive, suppressive, stimulatory, and preparative. All of these functions can be identified in the action of glucocorticoids (and stress in general) on the immune system. In addition, permissive and suppressive effects of glucocorticoids on different molecules involved in a particular immune function may produce a bell-shaped dose–response curve [17]. We observed such a curve in the case of the IgM antibody response to the T-dependent antigen, sheep erythrocytes [63]. However, most immunological parameters in our studies have exhibited linear dose–response relationships [63,64,96]. This suggests the possibility that pharmacological intervention during stress responses to limit (but not eliminate) increases in glucocorticoid concentration may diminish adverse effects without eliminating the adaptive benefits of the stress response.

Although the actions of glucocorticoids and other mediators in stress responses are clearly complex and not fully understood, pharmacological intervention to ameliorate the harmful effects of particular stress-related mediators on the immune system and nervous system seems possible. Agents that decrease glucocorticoid synthesis are promising in this regard,

because the dose can be adjusted to minimize effects on basal glucocorticoid levels, and because some drugs with this effect are already in use in humans [103,104]. In fact, glucocorticoid synthesis inhibitors have already been used with some success in the treatment of depression [105].

It is often assumed that the protective/beneficial effects of stress-induced hormones are derived from the increased concentrations of these hormones associated with stress responses. However, in some cases, this assumption is based on the observation that drastically decreasing concentrations of some of these hormones (e.g., by adrenalectomy) renders animals more sensitive to the lethal effects of a variety of stressors. However, Whitnall [106] noted that this assumption is often unwarranted and that basal levels of stress-related hormones may be sufficient to confer protective effects. This is the case with regard to a virus-induced, cytokine-mediated shock syndrome in mice [14], but perhaps not for the development of experimental allergic encephalomyelitis [43]. Nevertheless, it may be possible to regulate stress-induced glucocorticoid levels to prevent some of the associated deleterious effects, without seriously compromising most protective effects, particularly if the duration of treatment could be limited.

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